Multi-feature function-on-scalar regression for modelling stepwatch activity data

by

Hanying Li

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Abstract

In this thesis, we propose to use function-on-scalar regression models for modeling summaries derived from minute-to-minute step count data collected with Stepwatch^{TM} Activity Monitor (SAM). The approach has been motivated by the OUTLET study that compares the transtibial amputation vs limb salvage and use SAM as an objective measure of the 18 month functional outcomes. We compare both daily summaries and temporal change in the day of different measures of walking activities of amputee and salvage groups. On the whole, amputation and salvage treatments for severe distal, tibia, ankle and/or foot trauma result in comparable functional outcomes measured with step activity monitors. However, most of the summaries that measure the stability and variability of walking activity are significantly influenced by amputation, at least for a period of time in the day.

Keywords: functional-on-scalar regression models, Stepwatch^{TM} Activity Monitor, transtibial amputation, limb salvage

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Table of Contents

List of Tables

List of Figures

Chapter 1

Introduction

Several factors influence the decision whether to amputee or reconstruct a leg that is severely injured. While limb salvage is technically feasible in most cases, it may not always be advisable [1]. In particular, studies suggest that patient outcomes following severe injury to the foot or ankle may actually be better under amputation versus limb salvage [2]. These studies, however, rely for the most part on patient reported outcomes of function and limited measures of performance under ideal conditions (i.e. in the setting of a clinic). The Major Extremity Trauma Research Consortium (METRC) is conducting a study to compare 18 month functional outcomes (including performance measures of agility, strength and balance) and patient reported measures of health related quality of life (HRQoL) for a cohort of patients undergoing limb salvage versus amputation following severe distal tibia, ankle and/or foot injuries (the OUTLET study). To address the limitations of previous studies, the OUTLET study is also objectively measuring physical activity in everyday life using the Stepwatch^{TM} Activity Monitor (SAM) (StepWatch, Orthocare, Mountlake Terrace, WA) [3, 4]. Participants are asked to wear the SAM for 14 consecutive days at 18 months following their injury.

Wearable devices for measuring various physical activity parameters such as steps have become more and more popular both in epidemiological and clinical studies as well as among regular fitness- and health-conscious consumers interested in better quantification their daily life [5]. Ambulatory monitoring of physical activity has many advantages over traditional in-lab performance measures. Compared to in-lab measures that observe subjects in a short period of time, activity trackers allow real-time monitoring and thus are able to provide a fuller picture of functioning in real-life context [6]. The accuracy, precision, and medical benefit of currently available fitness trackers have been widely reported [7, 8].

Current methods for analyzing minute-by-minute activity data collected with step counters fall well short of the sophistication of the data, often relying on simple multi-day averages or the total volume of time spent doing light, moderate or vigorous step activity. The latter heavily depends on cut-points and may be inappropriate in particular clinical populations. There are two important issues regarding the current analytical practice. First, a major consequence of collapsing daily information into an average is a loss of many features beyond average step activity , which may be vitally important. For example, features describing the number and duration of activity bouts (uninterrupted periods of activity) or the fragmentation of step activity profiles with respect to rest/activity can be very informative and may provide a much fuller picture of the patient's function and level of activity. Second, the information about the temporal distribution of step activity over the course of a day can be essential to identify potential differences in circadian/diurnal patterns of step activity.

Motivated by the minute-by-minute step count data collected in the OUTLET study, we propose a flexible modeling framework based on function-on-scalar regression models [9, 10] that address both issues and allows a modeling of the temporal patterns of multiple features describing various aspects of step activity over a course of a day. Particularly, we will quantify the walking activity of OUTLET participants through 15 summary measures derived from the SAM data (step counts) during 6AM to 12AM time period and compare those measures between amputation and salvage treatments.

Chapter 2

Study Design

Stepwatch$^{\mathrm{TM}}$ Activity Monitor (SAM) is a small pager sized device that is worn by a patient around the ankle [3]. It counts the number of steps taken by the wearer at minute level. The device is well validated in amputation and foot and ankle disability research [3].

We have analysed SAM data collected by the end of February of 2016. By that time, the study has collected data on 142 limb salvaged patients and 34 limb amputated patients across all METRC cites. SAM activity were obtained at 18 months following injury. The age range was 18 to 60 years old (y.o.) with a mean of 39.5 y.o. and a standard deviation of 12.44. Each subject wore the SAM device for a two-week sample period. Minute-level SAM data for each subject have been processed in R and stored in $1440 \times D_i$ matrices, where 1440 represents the number of minutes in a day and D_i is the number of valid days provided by subject i.

There was a baseline hospital interview for all patients. During the interview, information including gender, age, weight, current employment status, current working time, amputation status, race or ethnicity, primary occupation, height, body mass index (BMI) was collected. In addition, the weight bearing and ambulatory status was investigated in follow-up interviews.

SAM lacks the function of detecting whether it is worn or not [3]. Therefore, patients were encouraged to provide a self-reported take on/off log that records the date and time when they took on and took off the device. 43 out of 176 patients submitted the self-reported log.

Chapter 3

Summaries of Walking Activity

3.1 Measures of daily walking activity

In this section, we review and discuss the measures of walking activity that will be used in our analysis. Conceptually, these measures can be grouped into three categories: i) statistical measures that quantify the average level of step activity and variability about this level; ii) maximal measures that quantify the maximum levels of activity recorded in free-living settings; and iii) measures of stability and variability that describe temporal change of the activity. The comprehensive list of measures will be explored to fully characterize multiple aspects of walking activity represented by the high dimensional activity profiles consisting of 1440 minute-to-minute for every single day.

Statistical measures

We start with the statistical measures. For subject i during day j, we defined the total step activity count as

$$total.stat = \sum_{t=1}^{n} x_{ij}(t) = \mu * n, \tag{3.1}$$

where μ is the mean count. The standard deviation and the coefficient of variation are defined as

$$sd.stat = \sigma = \sqrt{\frac{1}{n}\sum_{t=1}^{n}(x_{ij}(t) - \mu)^2} \tag{3.2}$$

and

$$coefvar.stat = \frac{\sigma}{\mu}, \tag{3.3}$$

respectively.

The above statistical measures are unconditional and do not differentiate between active and non-active time. To address that, we introduce additional measures. The number of active minutes is defined as

$$num.actmins = \sum_{t=1}^{n} I(x_{ij}(t) > 0) \tag{3.4}$$

and the mean step count during active time as

$$act.mean = \mu^a = \frac{\sum_{t:x_{ij}(t)>0} x_{ij}(t)}{\sum_{t=1}^{n} I(x_{ij}(t) > 0)}. \tag{3.5}$$

We can also define standard deviation during active time as

$$act.sd = \sigma^a = \sqrt{\frac{1}{n}\sum_{t=1}^{n}(x_{ij}(t) - \mu)^2} \tag{3.6}$$

Maximal measures

Now, we will introduce metrics that measure maximum walking capacity shown in the free-living environment. The first one is the sum of the top 10 minute-level step counts

$$max10.sum = \sum_{r=n-9}^{n} x_{ij(r)}, \tag{3.7}$$

where $\{x_{ij(r)}\}$ is the order statistic of $\{x_{ij}(t), t = 1, 2, \cdots, n\}$. The second one is the maximum walking activity in a continuous 6-minute window

$$max6.sum = \max_{p=1,2,\cdots,n-5} \left\{ \sum_{t=p}^{p+5} x_{ij}(t) \right\}. \tag{3.8}$$

Measures of stability and variability

Finally, to measure how stable the walking patterns are, we introduce a few measures of stability and variability.

The variability of the velocity can be calculated as

$$total.var = \frac{n \sum_{t=2}^{n} (x_{ij}(t) - x_{ij}(t-1))^2}{(n-1) \sum_{t=1}^{n} (x_{ij}(t) - \mu)^2}. \tag{3.9}$$

Note that we have normalized it by standard variation. An acceleration rate can be estimated as

$$accel.rate = \frac{\sum_{t:x_{ij}(t)-x_{ij}(t-1)>0} (x_{ij}(t) - x_{ij}(t-1)}{\sum_{t=2}^{n} I\{x_{ij}(t) - x_{ij}(t-1) > 0\}}. \tag{3.10}$$

i.e., the average positive change in step counts. Similarly, a deceleration rate can be defined as

$$decel.rate = \frac{\sum_{t:x_{ij}(t)-x_{ij}(t-1)<0} (x_{ij}(t) - x_{ij}(t-1)}{\sum_{t=2}^{n} I\{x_{ij}(t) - x_{ij}(t-1) < 0\}}. \tag{3.11}$$

Then, it is naturally to define the ratio of acceleration and decelerate rate as

$$accel.ratio = \frac{accel.rate}{decel.rate}. \tag{3.12}$$

The number of active and non-active bouts can be used to measure how fragmented the daily patterns of activity are. An active bout is defined as a a continuous period of activity [9]. An inactive bout is similarly defined as a continuous period of time with no walking activity. Let n_a be the number of active bouts and n_r be the number of inactive bouts. Note that $|n_a - n_r| \leq 1$ is always true. Therefore, we will only analyze n_a

$$act.bouts = n_a. \tag{3.13}$$

More bouts usually leads to shorter duration of each of them. We will measure that through the average duration of active and non-active bouts as [9]:

$$act.dur = \frac{\sum_{t=1}^{n} I(x_{ij}(t) > 0)}{n_a} \tag{3.14}$$

$$inact.dur = \frac{\sum_{t=1}^{n} I(x_{ij}(t) = 0)}{n_r}. \tag{3.15}$$

Log-transformation of original data

Many of walking measures discussed above will follow non-symmetric distributions, so, we will log-transform them whenever it is needed. Particularly, *total.stat*, *coefvar.stat*, *num.actmins*, *max6.sum*, *accel.rate*, *decel.rate*, *act.bouts*, *act.dur*, *inact.dur* [11]. The log transformation is calculated as $\log(x+1)$, where x is a metric. The metric names are prefixed with *log.* as the new metric names. For example, $log.total.stat = \log(total.stat + 1)$ is the log-scaled *total.stat*.

3.2 Wear-time detection

According to the self-report logs, some subjects took off the device to take a shower or go to sleep, and the corresponding periods show 0 steps. That is, steps could occur even when the SAM record is 0. As a result, it is very important to determine whether a subject was wearing the device when no steps was recorded, or whether the steps were true positive. Our solution is to use function `accel.weartime` in R Package `accelerometry` [12], which identifies periods of non-wear time in minute-to-minute accelerometer data.

The function supports the following parameters:

`window`: Minimum length of a non-wear interval

`tol`: Number of minutes with non-zero counts allowed during a non-wear interval

`tol.upper`: Maximum count value for a minute with non-zero counts during a non-wear interval

The algorithm uses a moving window to go through every possible interval of length window in input vector counts [12]. Any interval in which no more than `tol` counts are non-zero, and those counts are less than `tol.upper`, is classified as non-wear time [12]. In addition, by default, the algorithm is applied on continuous basis for full monitoring period that does not distinct observed days every 1440 minutes [12].

In our analysis, we set $\texttt{window} = 90, \texttt{tol} = 0, \texttt{tol.upper} = 99$.

Manual check were conducted on the match of the self-reported take on/off records and the algorithm detected wear/non-wear time, which confirms an acceptable performance of the algorithm.

3.2.1 Valid Days

In the data, long periods of non-wear time were observed. Days with too much missing data fail to represent the walking activity style of the subjects; in subsequent analysis, these days will be dropped out. So we introduce the concept "valid day". We define a day to be a valid day if the wear-time is at least T_v minutes, i.e. T_v is the threshold for a day to be classified as a valid day. In our analysis, we will test the sensitivity of the results to the particular threshold by setting $T_v = 120, 300, 600, 900$. If all monitored days of a subject are "invalid" for a particular value of the threshold, the subject will be eliminated from the analysis.

3.3 Profiles

To qualitatively evaluate the daily walking activity pattern and its day-to-day variability for each subject, we created two-panel visual profiles with a needle plot of the original minute-level data on the left panel and a day-by-day summaries presented at the right panel. As shown in Figure 3.1 right panel, the x-axis represents the observed dates with each row representing one summary. The height of the needles reflects the value of the summary on the specific day.

Figure 3.1 is a profile plot of ID 1021. In the left panel, the minute-to-minute steps are shown as needles with the height of the needles indicates the steps in that minute. Each row displays 1440 minutes from 12AM to 12AM in a natural day, and the number of rows corresponds to the number of days monitored. The plot also reveals the clinical information (all variables in the clinic information table) of the subject. Meanwhile, the area with pink background identifies the non-wear interval, and the blue colored minutes are wear time.

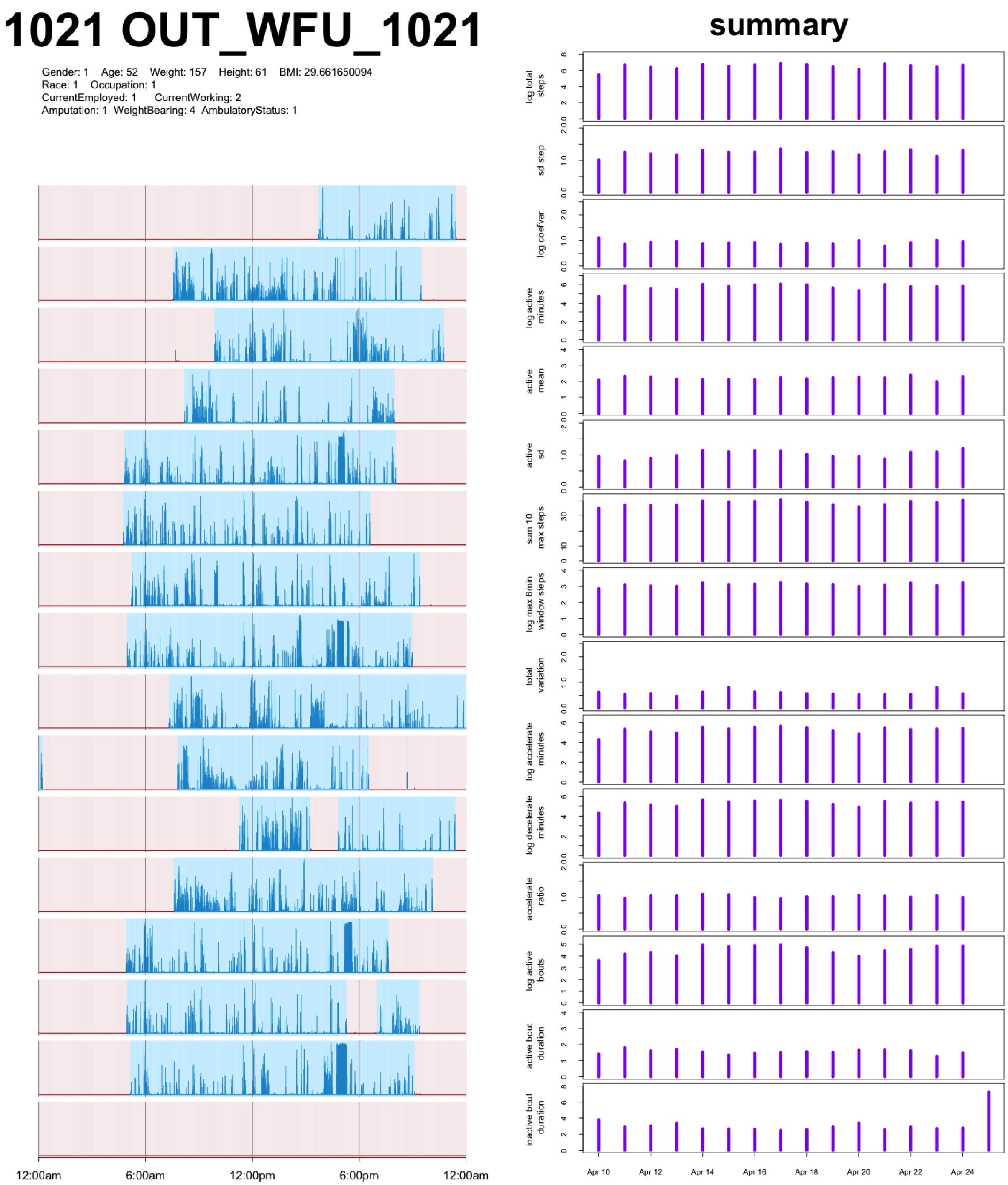


Figure 3.1: Profile plot for ID 1021

Chapter 4

Exploratory Analysis

Walking activity styles are closely linked to different periods of typical routine such as getting up, having meals, and working indoors. For instance, people are relatively sedentary before getting up, and will then experience a sharp increase in step counts when getting up. Compared to morning time, people may gain more fatigue in the evening and thus perform a lower level of walking activity. Naturally, it is interesting to test a hypothesis that amputees tend to be more likely to experience late-afternoon fatigue than salvages. If so, the difference of related summary statistics between the two groups should show a trend that depends on the time of day. Therefore, we created metrics to represent the "temporal" change of the features introduced in the previous chapter.

4.1 2-hour moving windows and metrics

Each day was split into moving 2-hour windows starting from 12AM-2AM and ending at 10PM-12AM with a half an hour moving steps. That is, the first 2-hour window is 12AM-2AM, then 12 : 30AM-2 : 30AM, 1AM-3AM, and so on. For each of these 45 windows, summaries introduced in the previous chapter were calculated, where the length of the time interval (n) was set to 120 minutes. Notice that two adjacent windows have 90 minute overlap resulting in "smoothed" changes between windows.

4.2 Subject specific average summaries

Next, we summarize the data structure after the pre-processing steps outlined above. For each subject, there are 14 monitored days, among which some are not valid days. Within each day, there are 45 2-hour windows, and 15 summaries are calculated to represent the walking activity within each window. For each time window and a metric of interest, we used the mean over all valid days as the representative summary at the time window for the subject.

The subsequent analyses of the measures heavily rely on symmetric distribution of the outcomes. We checked the distributions of subject specific average summaries in 12 non-overlaping windows [13]. Figure 4.1 contains the distribution plots of *num.actmins* and *act.bouts* under valid day threshold equal to 600 minutes. The y-axes in each subgraph denote the time windows in 24-hour time system. Two observations can be drawn from these figures:

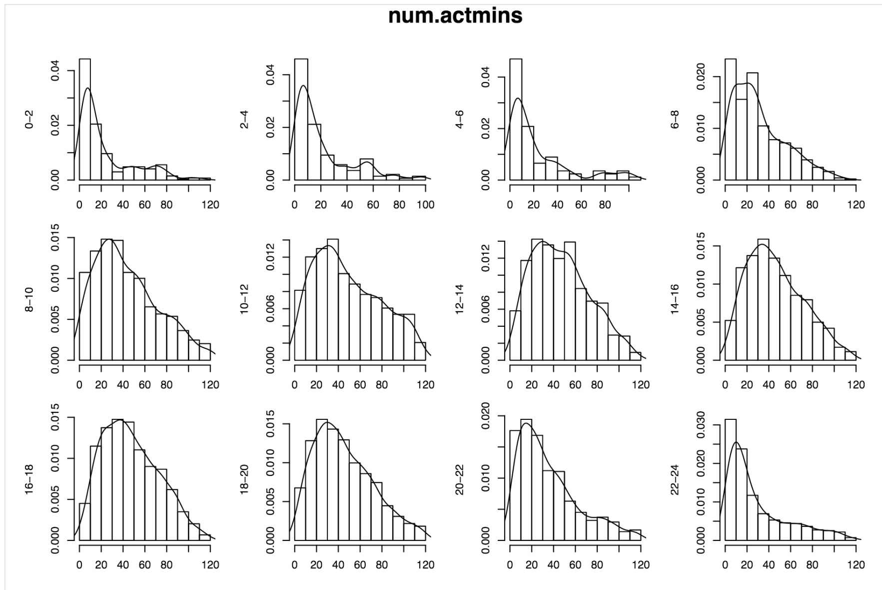
1. Time windows from 12AM to 6AM have distinct distribution feature compared to the rest of the day. For both *num.actmins* and *act.bouts*, the modes are skewed to 0 in the first 3 subgraphs. It is reasonable to assume that this is a consequence of late-night activity. Particularly, the period of 12AM-6AM is the time when most people are sleeping and thus having 0 step count. In addition, subjects who got up before 6AM and those who stayed up contribute to the bi-distribution of *num.actmins*.

2. It is important to note that many time windows in the 6AM-12AM period, the distributions are not necessarily approximately normal, thus proper transformation on the metrics are required.

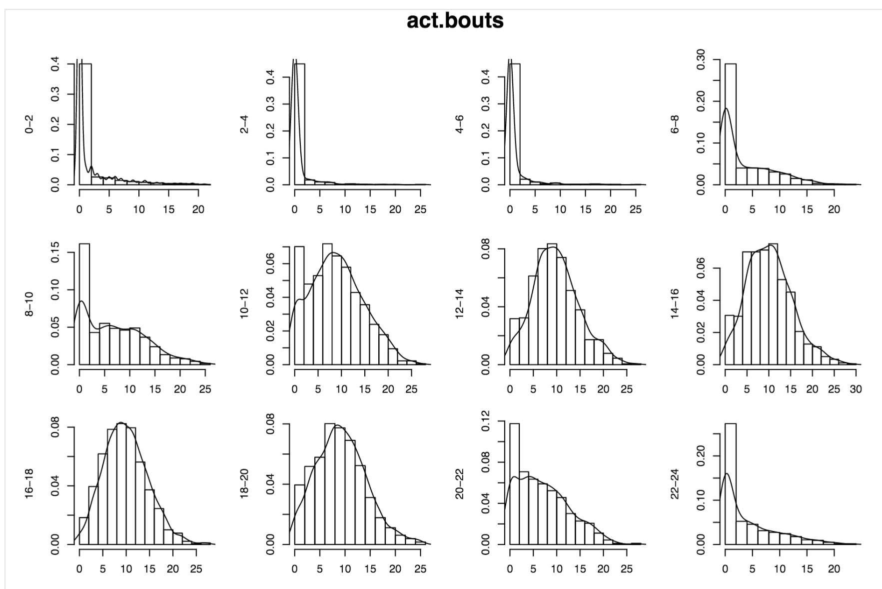
Consequently, windows containing 12AM to 6AM were excluded from the analysis because of the inability to provide evidence of different walking activity styles between the salvage and amputee groups. Therefore we used totally 33 2-hour windows from 6AM to 12AM. In addition, a log transformation was applied to summaries that do not follow a symmetric distribution.

4.3 Late night activity

Although we dropped 6AM-12AM windows, there is a late night activity observed in some of the subjects. To account for the differences among morningness/eveningness chronotypes, we created a late-night activity indicator variable for each subject that was set to 1 has on average more than 60 steps during 12AM-6AM, and 0, otherwise.



(a) Distributions of subject specific average number of active minutes



(b) Distributions of subject specific average number of active bouts

Figure 4.1: 2-hourly summary distributions under 600-minute valid day threshold

Chapter 5

Multifeature Function-on-Scalar Regression Model

To compare two treatments, we will start with scalar linear regression models with the daily summaries of walking activity as outcomes. All models have been adjusted for baseline age, gender, current employment status, amputation status, body mass index (BMI), and late-night activity. We will then propose multifeature function-on-scalar regression models [10] and explore how the summaries change with the time of a day.

5.1 Characteristics associated with subject-specific mean daily summaries

We start with exploring the association between the amputation status and subject-specific mean daily summaries adjusting for baseline age, gender, current employment status, body mass index (BMI), late-night activity, and interaction of amputation status and late-night activity. Figure 6.1 reports the significance or non-significance of p-values of the amputation status variable and indicate the difference between the groups according to the specific summary.

We will discuss all results in the next section.

Note that the subject-specific mean daily summaries were sensitive to the choice of the threshold defining the valid day.

5.2 Functional-on-scalar regression model

As mentioned above, walking activity patterns change over the time of a day. The daily features, motivated by the idea of summarizing the 1440-minute step counts in a single quantitative values, actually sacrificed thousands of data points to simplicity. It is always a problem to balance the retention of raw data details and the generality of the statistics. Consequently, the functional-on-scalar regression model is proposed to monitor the effects of walking activity related characteristic changing over time.

5.3 Statistical framework

Let $y_i(t)$ be the response for subject i at time t, and $\boldsymbol{x}_i = (x_{i,1}, x_{i,2}, \cdots, x_{i,p})$ be a vector of covariates for subject i. A functional-on-scalar regression model can be formulated as

$$y_i(t) = \mu(t) + \boldsymbol{x}_i\boldsymbol{\beta}(t) + \epsilon_i(t) = \mu(t) + \sum_{k=1}^{p} x_{i,k}\beta_k(t) + \epsilon_i(t),$$

in which $\beta_k(t)$ are effect coefficient functions corresponding to the scalar covariates $x_{i,k}$, $\mu(t)$ is the intercept function or the mean effect, and $\epsilon_i(t)$ is a subject-specific random deviation from the effect mean structure. Assume that functions are observed on a common grid $\{t_j, 1 \leq j \leq J\}$. A reasonable assumption for the random effect $\epsilon_i(t)$ is that $\epsilon_i(t)$'s are independent across subjects.

The model fit can be intuitively described as a two-step approach. First, for each t_j, fit the linear regression

$$y_i(t_j) = \mu(t_j) + \sum_{k=1}^{p} x_{i,k}\beta_k(t_j) + \epsilon_i(t_j),$$

and denote the resulting estimates as $\tilde{\mu}_j$ and $\tilde{\beta}_{k,j}$. Then smooth $\{\tilde{\mu}_1, \cdots \tilde{\mu}_J\}$ to obtain $\hat{\mu}(\cdot)$ and $\{\tilde{\beta}_{k,1}, \cdots, \tilde{\beta}_{k,J}\}$ to obtain $\hat{\beta}(\cdot)$.

In our analysis of OUTLET data, the response $y_i(t_j)$ is a subject-specific mean summary (e.g. *log.total.stat*) for subject i at the jth 2-hour window, where $j = 1, 2, \cdots, J = 33$. Amputation status, age, gender, current employment status, centered BMI at 25, late-night activity, and interaction between amputation status and late-night activity are also included in the model. The multifeature functional-on-scalar regression model takes into account the time of a day and multiple features of walking activity. However, note that by the use of subject-specific mean summaries, the day-to-day variability (multiple days within a subject) is fully ignored and could be a topic of future research.

The analyses were performed in R, by function `fosr` in package `refund` [14]. We used penalized generalized least squares (GLS) as the estimate method, and restricted maximum likelihood (REML) as the smoothing parameter selection method.

Finally, two technical details need to be mentioned. First, in `fosr` function, the functional responses are given as an $N \times J$ matrix Y, where N is the number of repeated observations and J is the number of observed time grids. Given a valid day threshold, N is the number of subjects having at least one valid day, J is 33, the number of 2-hour windows. Second, `fosr` function does not allow missing values in the Y matrix. However, due to the non-wear time in the data collection, there is probability of missing values in the subject-specific summaries. We interpolated the missing summaries with the group mean (amputee or salvage) of the metric in that time window.

Chapter 6

Results

First, we describe demographics of our clinical sample. The 34 amputee subjects consist of 6 females and 28 males with age ranging from 20 years to 62 years with a mean of 41.79, and a mean BMI of 30.79 kg/m^2. 44.1% of the amputees were employed at the baseline visit. 44.4% of the salvages are female, 51.5% were employed. Similar to the amputee group, salvages have a mean baseline age of 40.09 years and a mean body mass index of 30.75 kg/m^2.

Scalar model of daily summaries

Table 6.1 reports the number of subjects and number of all valid days for salvage and amputee groups included in the model under four thresholds.

Threshold	Amputee	Valid days (amputee)	Salvage	Valid days (salvage)
120	33	430	142	1626
300	32	377	141	1482
600	29	252	133	1076
900	22	76	73	297

Table 6.1: Number of subjects and number of all valid days in salvage and amputee groups under different valid day thresholds

A higher threshold indicates more accuracy of the original data and more credibility of the derived summary statistics, but also results in fewer valid days that may translate into a larger variance for the subject-specific summaries within each subject. Since the response in the functional-on-scalar models are the subject-specific summaries, the number of subjects is more important than the number of valid days. Taking both concerns into account, we display main findings on the 600-minute threshold basis afterwards.

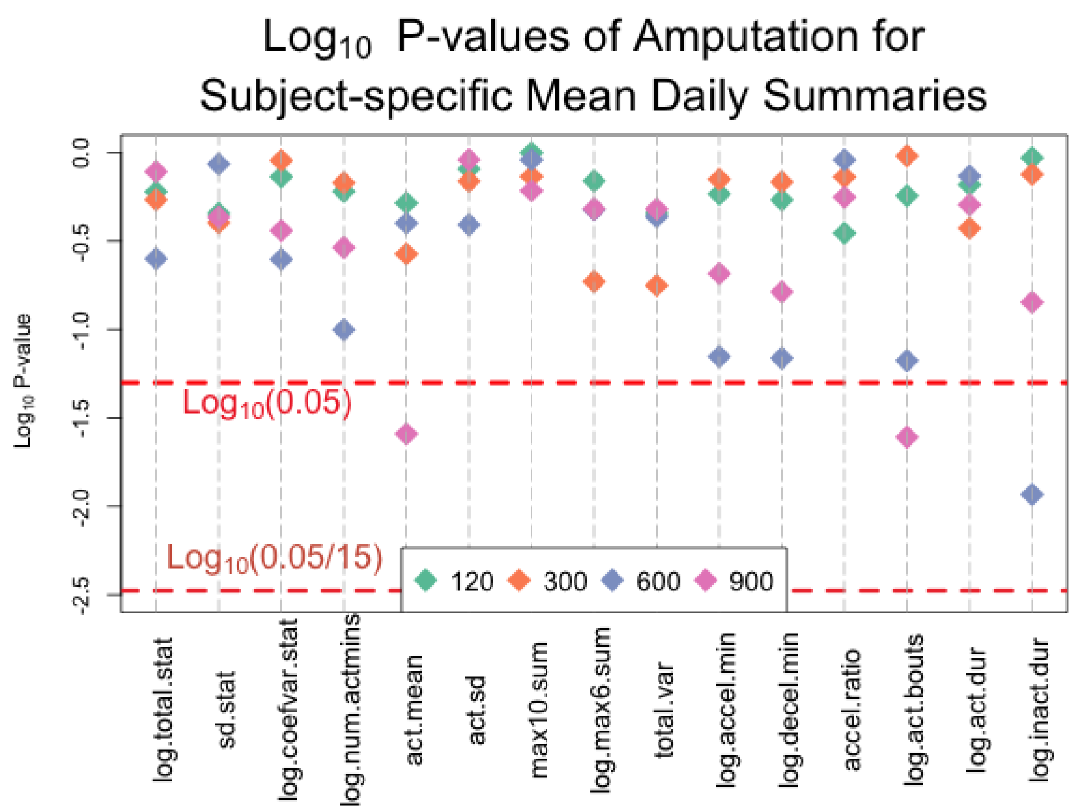


Figure 6.1: $\log_{10}$ p-values of amputation status for subject-specific mean daily summaries under different valid day thresholds.

Table 6.2: Simple linear regression coefficients for amputation status on subject-specific mean daily summaries under 600-minute valid day threshold - 1.

	log.total .stat	sd.stat	log.coefvar .stat	log.num .actmins	act.mean
age	0.0001	0.0004	0.0003	−0.001	0.002
	(0.003)	(0.001)	(0.001)	(0.002)	(0.002)
gender	−0.03	0.02	0.01	−0.05	0.04
	(0.07)	(0.03)	(0.03)	(0.06)	(0.04)
amputation	0.13	−0.01	−0.05	0.15	−0.06
	(0.11)	(0.04)	(0.04)	(0.09)	(0.07)
nightact	0.19*	0.04	−0.04	0.16*	0.06
	(0.07)	(0.03)	(0.03)	(0.06)	(0.05)
Employed	0.35**	0.14**	−0.09**	0.27**	0.14**
	(0.07)	(0.03)	(0.02)	(0.05)	(0.04)
bmi25	−0.01**	−0.01**	0.004*	−0.01*	−0.01**
	(0.004)	(0.002)	(0.002)	(0.003)	(0.003)
amputation:nightact	−0.26	−0.07	0.09	−0.21	−0.10
	(0.17)	(0.07)	(0.06)	(0.14)	(0.11)
Constant	6.25**	1.07**	0.94**	5.55**	2.03**
	(0.13)	(0.05)	(0.05)	(0.11)	(0.08)
Observations	158	158	158	158	158
R^2	0.25	0.25	0.14	0.23	0.18
Adjusted R^2	0.22	0.22	0.10	0.19	0.14
Residual Std. Error (df = 150)	0.40	0.16	0.15	0.33	0.25
F Statistic (df = 7; 150)	7.27**	7.18**	3.58**	6.39**	4.70**
Note:					*p<0.05; **p<0.003

Table 6.3: Simple linear regression coefficients for amputation status on subject-specific mean daily summaries under 600-minute valid day threshold - 2.

	act.sd	max10.sum	log.max6 .sum	total.var	log.accel .min
age	−0.0004	−0.01	−0.0000	0.0003	−0.0004
	(0.001)	(0.01)	(0.001)	(0.001)	(0.002)
gender	0.003	−0.09	0.02	−0.03	−0.06
	(0.01)	(0.38)	(0.02)	(0.02)	(0.05)
amputation	−0.02	0.07	−0.02	0.03	0.15
	(0.02)	(0.62)	(0.03)	(0.04)	(0.08)
nightact	−0.01	0.49	0.02	−0.04	0.15*
	(0.01)	(0.41)	(0.02)	(0.03)	(0.05)
Employed	0.07**	2.34**	0.09**	−0.09**	0.23**
	(0.01)	(0.36)	(0.02)	(0.02)	(0.05)
bmi25	−0.002*	−0.09**	−0.004**	0.002	−0.01*
	(0.001)	(0.02)	(0.001)	(0.001)	(0.003)
amputation:nightact	0.02	−0.74	−0.001	0.04	−0.19
	(0.03)	(0.93)	(0.05)	(0.06)	(0.12)
Constant	0.89**	36.43**	3.00**	0.60**	5.04**
	(0.03)	(0.72)	(0.04)	(0.05)	(0.09)
Observations	158	158	158	158	158
R^2	0.22	0.30	0.25	0.16	0.23
Adjusted R^2	0.18	0.27	0.22	0.13	0.19
Residual Std. Error (df = 150)	0.08	2.22	0.11	0.14	0.29
F Statistic (df = 7; 150)	6.00**	9.23**	7.21**	4.22**	6.37**

Note: *p<0.05; **p<0.003

Table 6.4: Simple linear regression coefficients for amputation status on subject-specific mean daily summaries under 600-minute valid day threshold - 3.

	log.decel .min	accel .ratio	log.act .bouts	log.act .dur	log.inact .dur
age	−0.0003	0.0001	−0.0001	0.001	0.002
	(0.002)	(0.0002)	(0.002)	(0.002)	(0.002)
gender	−0.06	0.001	−0.07	0.02	0.07
	(0.05)	(0.01)	(0.04)	(0.04)	(0.05)
amputation	0.15	−0.001	0.13	−0.02	−0.22*
	(0.08)	(0.01)	(0.07)	(0.07)	(0.09)
nightact	0.15*	0.002	0.04	0.12*	−0.07
	(0.05)	(0.01)	(0.05)	(0.05)	(0.06)
Employed	0.24**	0.003	0.10*	0.14**	−0.18**
	(0.05)	(0.005)	(0.04)	(0.04)	(0.05)
bmi25	−0.01*	0.0002	−0.003	−0.003	0.01**
	(0.003)	(0.0003)	(0.003)	(0.003)	(0.003)
amputation:nightact	−0.18	0.01	0.01	−0.19	0.09
	(0.12)	(0.01)	(0.11)	(0.11)	(0.13)
Constant	5.03**	0.99**	4.15**	1.53**	3.04**
	(0.09)	(0.01)	(0.08)	(0.09)	(0.10)
Observations	158	158	158	158	158
R^2	0.23	0.02	0.09	0.16	0.18
Adjusted R^2	0.20	-0.02	0.04	0.12	0.14
Residual Std. Error (df = 150)	0.29	0.03	0.26	0.26	0.31
F Statistic (df = 7; 150)	6.58**	0.53	2.02	3.99**	4.66**

Note: *p<0.05; **p<0.003

Figure 6.1 displays $\log_{10}$ scaled p-values for the estimated amputation status variable corresponding to subject-specific mean daily walking activity metrics under different thresholds. Amputation was considered to be significantly associated with the metrics if the p-value was smaller than 0.05 or 0.05/15, where 15 is the number of daily summaries. It can be seen that $120-$ and $300-$minute valid day thresholds do not suggest difference between amputated and salvaged patients. Amputation status is observed to be a significant risk factor to *act.mean* and *log.act.bouts* under 900-minute valid day threshold, and *log.inact.dur* under 600-minute threshold.

Functional-on-scalar model of 2-hourly summaries

Estimated coefficient functions from FOSR together with the 95% confidence intervals are shown at Figures 6.2 – 6.4. Each coefficient function plot has 10 sub-figures. The first and second rows represent $\mu(t)$ and $\beta(t)$'s corresponding to covariates; the red line is the estimated functional effect and the black dash lines define the confidence interval. The bottom two graphs show the predicted summaries for a representative subject. The left one is for an unemployed 30-year-old female with a body mass index of 25 kg/m^2 who does not have late-night activity, and the right one is for an all-similar subject but has late-night activity. In both specific case plots, red solid and dash lines are estimated and confidence interval assumed that the woman is from the amputation group, while blue lines refer to the salvage group.

Amputation is considered to be a significant factor of a metric if the confidence interval of amputation effect coefficient for the metric does not cover

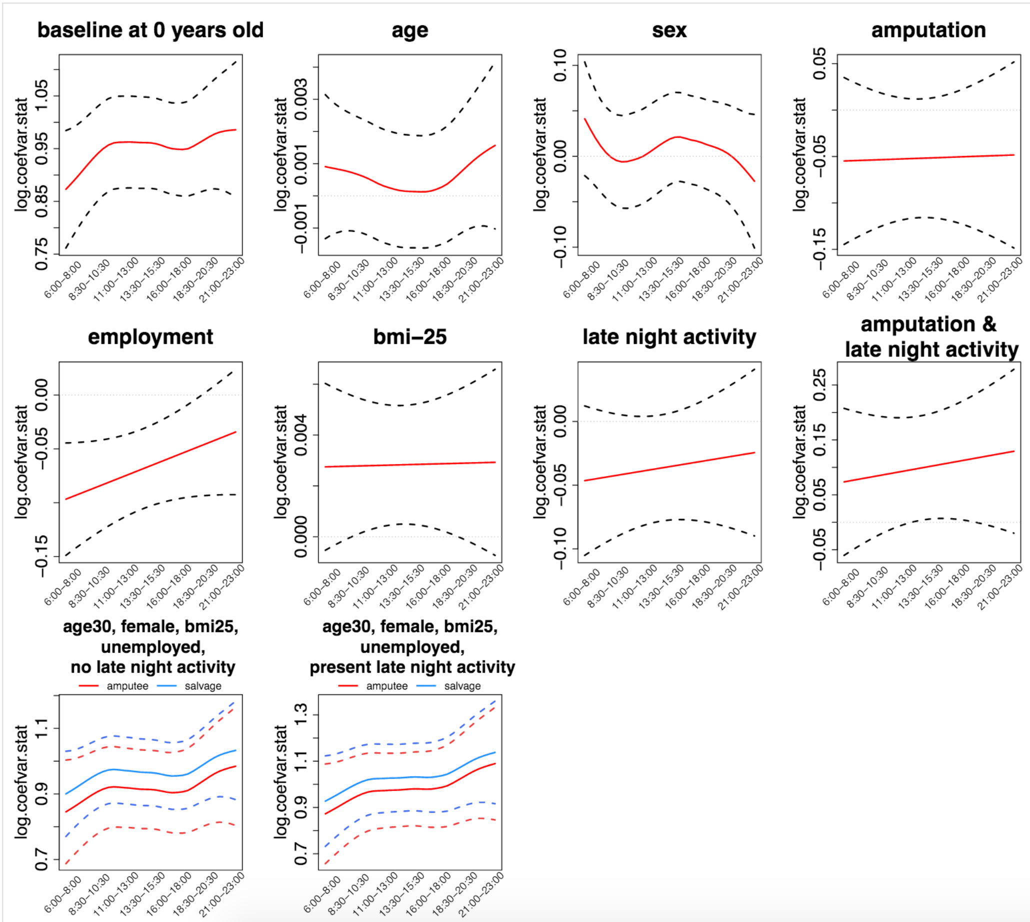


Figure 6.2: Time varying effect coefficient on log coefficient of variance (600-minute valid day threshold)

0. For example, in Figure 6.1, toward the end of a day, the amputation effect coefficient for the mean step count during active time ($act.mean$) is below 0, which means that in the evening, the amputee group is less active than the salvages when they are active. The feature can also be observed on the specific case plots for $act.mean$, where the red line is about 20% lower than the blue line at the end of the day. We could infer that amputees accumulates more fatigue than salvages from the day activities, thus cannot maintain the same level of

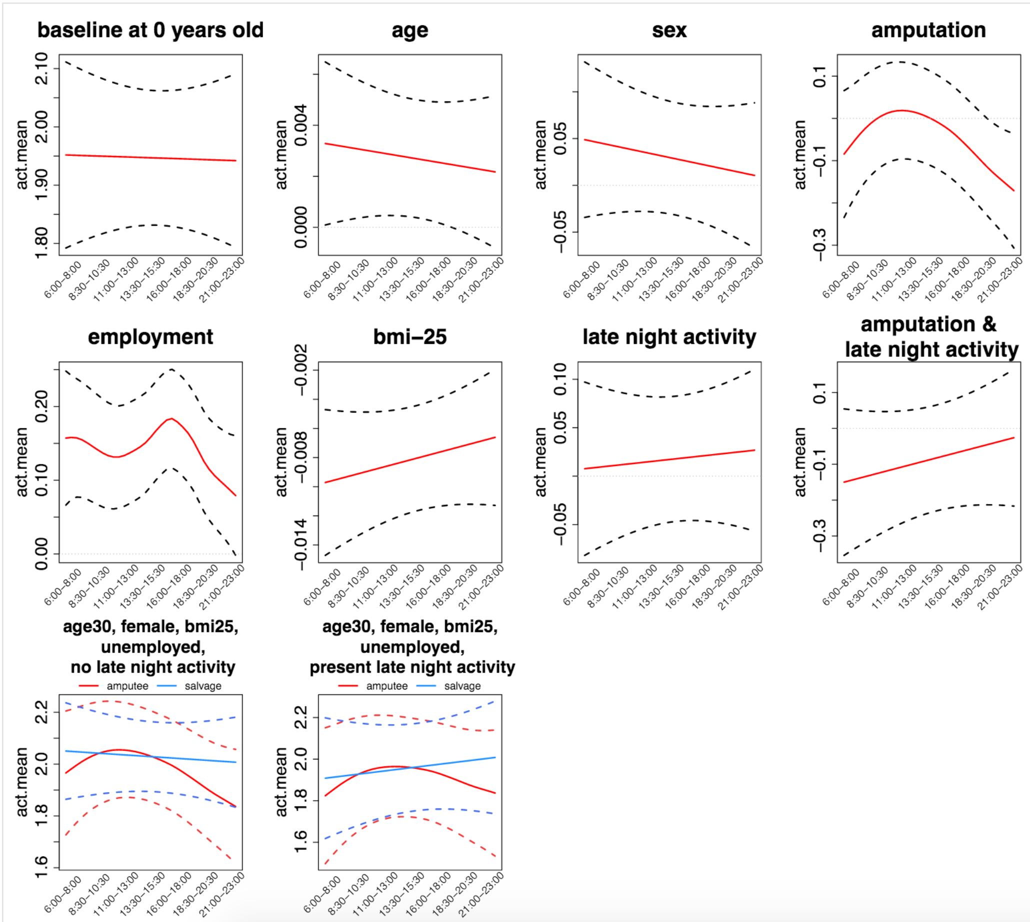


Figure 6.3: Time varying effect coefficient on mean step count during active time (600-minute valid day threshold)

activity as the salvages.

Similarly, we can make inference regarding the total variation presented at Figure 6.4. During the later half of a day, the amputation coefficient function is almost above 0. Recall that total variation measures the fragmentation of walking activity, thus in common words, during this period, amputees' walking activity more frequently switches between active and inactive.

Despite the exact difference between salvage and amputee groups at certain

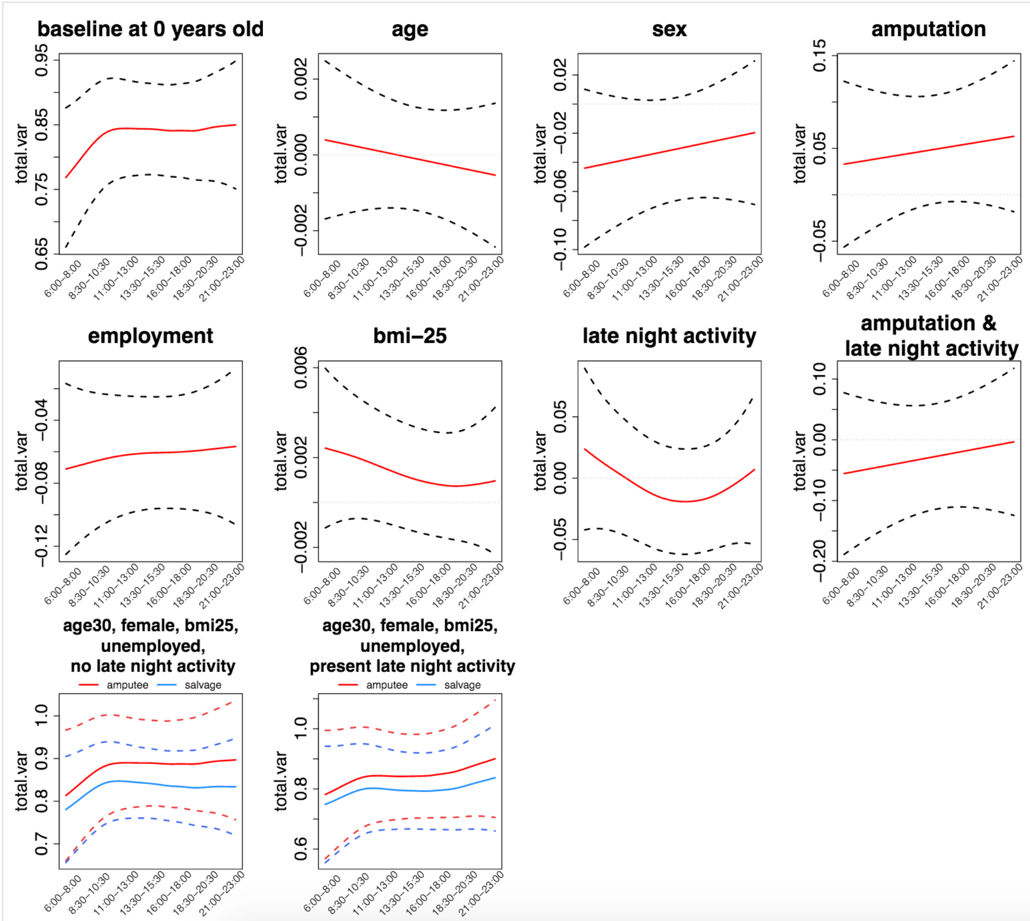


Figure 6.4: Time varying effect coefficient on total variation (600-minute valid day threshold)

time period, the plots also illustrate time trends of the difference of amputation effects. In Figure 6.2, the amputation effect on log coefficient of variance is almost a negative constant, therefore the dispersion of step count for amputees almost keeps a certain proportion of that for salvages from 6AM to 12AM. The amputation effect on mean step count during active minutes, however, is more sensitive to time. In the middle of the day, about noon time, there's no obvious difference between the two groups, and then divergence grows.

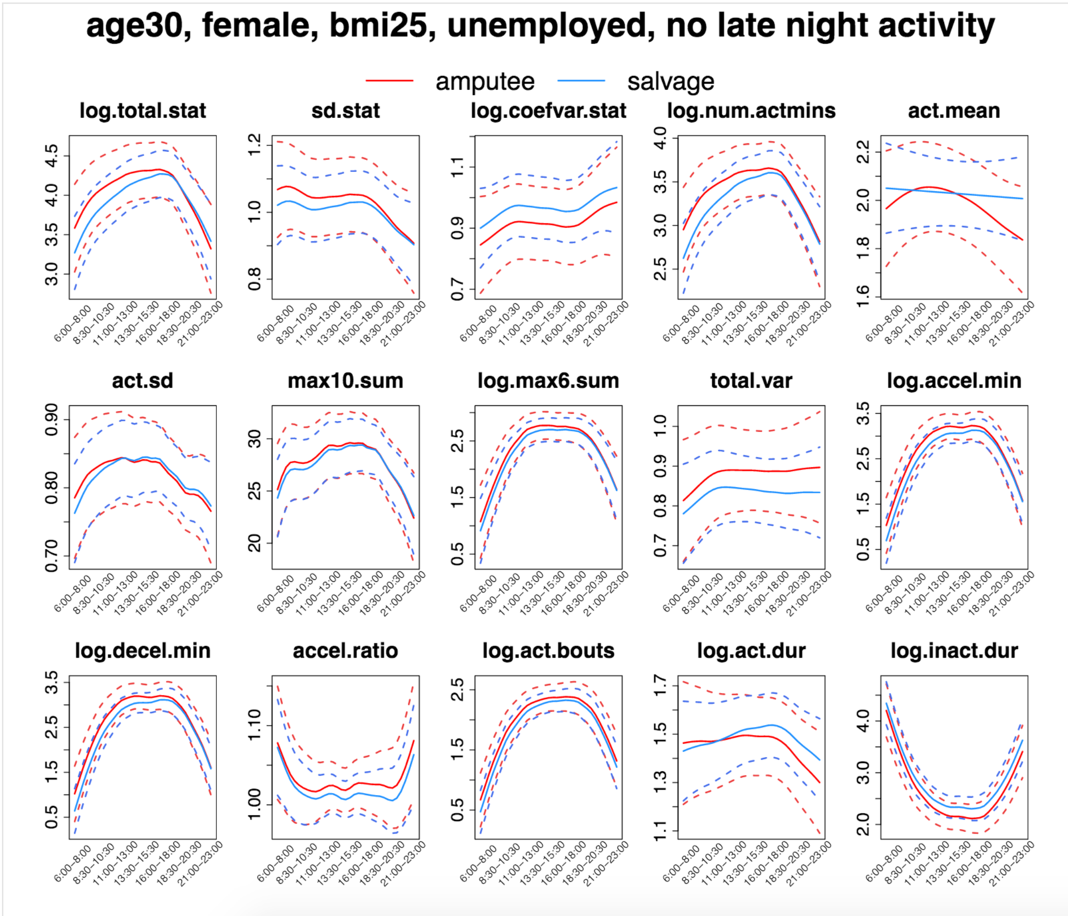


Figure 6.5: Predicted 2-hourly metrics moving per 30 minutes for a 30-year-old unemployed female with a BMI of 25, and without late night activity (600-minute valid day threshold).

Figure 6.5 – 6.6 displays the comparisons between amputation and salvage for all predicted metrics based on the specific cases, where Figure 6.5 is for a 30-year-old unemployed female with a BMI of 25, and without late night activity, and Figure 6.6 for a similar female but presents late night activity.

On the whole, amputation has a significant effect on most of the summaries that measure the stability and variability of walking activity and statistical measures, at least for a period of time in the day. Meanwhile, amputees and

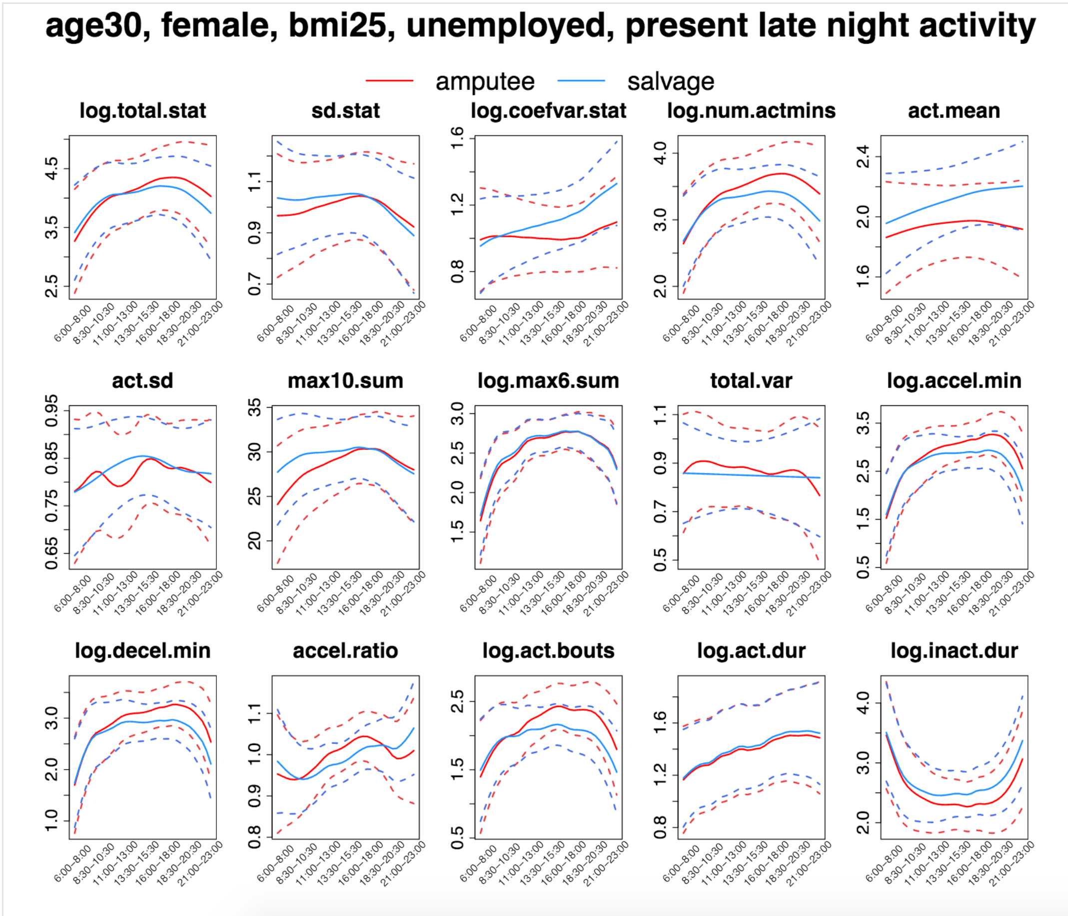


Figure 6.6: Predicted 2-hourly metrics moving per 30 minutes for a 30-year-old unemployed female with a BMI of 25, and presents late night activity (600-minute valid day threshold).

salvages have similar performance in terms of maximal measures.

Chapter 7

Conclusion

Based on the use of step watch, we investigated and compared walking activity between amputation and salvaged patients observed continuously over 2 weeks at the 18 month follow-up after surgeries. Besides the direct comparison of the original data collected by the device, we generated statistical measures, maximal measures, and measures of stability and variability of daily walking activity. Considering the possible influence of time of the day, we introduced the diurnal pattern composed of 2-hour metrics as the response functional response, and applied functional-on-scalar regression models on the functional response and scalar predictors.

Overall, amputated patients' walking activity is more fragmented than salvages. Amputees are also less active during active time, especially later in the day. It turns out that amputees experience higher levels of fatigue, but it does not affect the maximal levels of walking activity during the day.

Chapter 8

Discussion

8.1 Limitation and future work

Although our analyses take advantage of the functional-on-scalar regression models to estimate the amputation effect across day, there are a few limitations in our approach.

First, the long periods of non-wear time are present in the data. The self-reported log could be a solution to this issue, but not every subject provided an accurately reported log. The wear/non-wear detection algorithm, originally validated on healthy young adults, may be less appropriate for our clinical population. Meanwhile, the algorithm can only detect the false positive step counts, but can never compensate for the falsely flagged inactive periods.

Second, some of the 2-hourly summaries such as *max6.sum* have bi-model distribution that cannot be transferred to symmetric distribution. Accordingly, the functional-on-scalar regression model derived amputation effect coefficients may be unreliable. Therefore, the future work is needed to adapt mixtures of generalized linear models to handle situations like that.

Third, a sensitivity study on the selection of thresholds for valid day and late-night activity is still needed. Similarly, whether 60 step count during 12AM to 6AM is a robust cut off for the presence of late-night activity needs further analysis.

Our proposal for future work also includes the exploration of different summaries that may better reveal the overall difference between amputation and salvage groups, as well as recruiting more subjects in the amputation group - currently the samples are highly unbalanced with far fewer amputees than salvages.

8.2 Discussion

Our analysis shows that amputation and salvage treatments for severe distal, tibia, ankle and/or foot trauma result in comparable functional outcomes measured with step activity monitors. Based on OUTLET study design, the activity data has been collected at 18 months following injury, the expected time of full recovery from clinical perspective. Data collected over 14 consecutive days should be representative to accurate estimate of the real-life physical functioning. Therefore, the results of our analysis should be translatable to the general population of subjects experiencing severe distal, tibia, ankle and/or foot trauma.

Even though the amputee and salvage groups present very similar daily summaries, we can still draw significant difference when focusing on part of the day. In particular, we recommend to use *act.mean* and *log.coefvar.stat* at later half of the day as metrics of interest in related study.

In addition, our method can be used to identify subjects that are not fully recovered. The use of wearable technology enables the estimation of continuous/real-time trajectory of recovery.

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Appendix A

Full Plots Mentioned in Content

A.1 Profile Plots

We created profile plots for each subject and merged the plots by amputation/salvage groups.

A.1.1 Amputated patients

https://www.dropbox.com/s/8k6v4qukdmg9te9/profile_amputee_03.15.16.pdf?dl=0

A.1.2 Salvaged patients

https://www.dropbox.com/s/q0ncw27txnic9c8/profile_salvage_03.15.16.pdf?dl=0

A.2 Effect Coefficients Functions

We listed links to the 2-hourly summary distributions for all 15 metrics (full version of Figure 6.1 – 6.3) under different valid day thresholds.

A.2.1 120-minute

https://www.dropbox.com/s/k23htaheo90cjq8/thesis_2h-30window-refund_120.pdf?dl=0

A.2.2 300-minute

https://www.dropbox.com/s/cew3uc3vhxp1p1t/thesis_2h-30window-refund_300.pdf?dl=0

A.2.3 600-minute

https://www.dropbox.com/s/9ijf1acl41fuxgn/thesis_2h-30window-refund_600.pdf?dl=0

A.2.4 900-minute

https://www.dropbox.com/s/5s7ro8b8ilpoern/thesis_2h-30window-refund_900.pdf?dl=0

Vitae

Hanying Li was born August 30, 1992. in Jingmen, Hubei Province, China. She obtained her Bachelor's Degree of Science in Nanjing University in May, 2014. She then pursued Master of Science at Johns Hopkins Bloomberg School of Public Health from September, 2014. She started to work as a research assistant on the OUTLET project at Major Extremity Trauma Research Consortium (METRC) under supervision of Vadim Zipunnikov, PhD from July, 2015. She got a trainee position at the Welch Center for Prevention, Epidemiology, and Clinical Research in August, 2015, involving in research activities on CKD-PC study supervised by Morgan Grams, PhD. She was employed as a teaching assistant for course Methods in Biostatistics instructed by Daniel O. Scharfstein, ScD and Ingo Ruczinski, PhD, at Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, during September to December, 2015.